REMARKS

Claims 1-3, 5-6, 9-12, 19-36, and 44 are pending in this application. Claims 19-36 were withdrawn from consideration. Claims 1-3, 5-6, 9-12, and 44 are currently under examination; all claims have been rejected under 35 U.S.C. § 112, first paragraph.

By this amendment, claim 1 has been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification. Support for the amendment to claim 1 is found, *inter alia*, at page 11, lines 6 to 15, and page 12, lines 7 to 15.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-3, 5-6, 9-12, and 44 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention involves a method for providing dopamine or a dopamine precursor to the prefrontal cortex of the brain of a subject exhibiting certain symptoms of schizophrenia, through the administration of specified types of dopamine-producing cells coupled to

specified support matrices. The Examiner has rejected all pending claims as non-enabled, stating that the specification and the art at the time of filing do not provide specific guidance with regard to the claimed invention, which involves administration of cells that produce dopamine or a dopamine precursor. Specifically, the Examiner argues that the cells "must produce dopamine or a dopamine precursor at the appropriate location, in an amount sufficient to alleviate a symptom of schizophrenia," and that the "references cited do not provide evidence of an enabling disclosure for such a protocol." Pending Office Action of December 15, 2004, at 4. The Examiner attempts to distance the claimed invention from the enabling teachings of the art at the time of filing by asserting that although the art at the time of filing discloses cellular dopamine replacement therapy for *Parkinson's disease*, it does not provide guidance for treatment of a patient with *schizophrenia*, which has its own distinct etiology. Office Action at 4. The Examiner concludes that the "instant specification does not teach how to generate dopamine levels that are sufficient to reduce a symptom of *schizophrenia*." *Id.* (emphasis added).

Applicants respectfully submit that the amended claims are enabled, and would like to bring the following facts and points to the Examiner's attention:

- Contrary to the Examiner's view that cell-based therapy to the brain is a non-routine, undeveloped art that would require undue experimentation to implement, the art at the time of filing disclosed therapeutically effective, long term, dopamine expression through the administration of RPE cells with support matrix to the brain of patients suffering from Parkinson's disease.[1]

- The art at the time of filing teaches that administration of dopamine has a therapeutic effect on the negative symptoms of schizophrenia, and also teaches what amounts of dopamine precursors are needed for this. See, e.g., Inanaga et al, Folia Psychiatr. Neurol. Jpn (1975), 29:123-43 (disclosing that oral doses of 400-1200 mgs of levodopa are effective to alleviate negative symptoms of schizophrenia)

- The Examiner has not disputed that the art at the time of filing teaches that the cell-based therapies of this application generate levels of dopamine effective to treat Parkinson's

[1] For example, administration of dopamine producing cells adhered to matrix microcarriers to rodent and non-human primate models of Parkinson's disease resulted in long term amelioration of parkinsonian motor behavioral deficits. *See, for example*, U.S. Patent No. 5,618,531 (Cherksey *et al.*), of record; Potter et al. (1997) Abstracts Soc. for Neuroscience, 778:10; Subramanian et al. (1998) Abs. Amer. Soc. for Neural Transpl., 2-5; Subramanian et al. (1998) Abs. 5th International Cong. Parkinson's Disease and Movement Disorders, New York.

disease. And contrary to the Examiner's view, ***the art at the time of filing teaches that levels of dopamine or dopamine precursors that are effective to treat Parkinson's disease are also effective to treat the negative symptoms of schizophrenia***. Specifically, the dosage ranges for both diseases overlap. *Compare* Physician's Desk Reference (oral doses of 1-8 gm of levodopa for Parkinson's disease) with Inanaga et al, *Folia Psychiatr Neurol Jpn* (1975), 29:123-43 (oral doses of 400-1200 mgs of levodopa for negative symptoms of schizophrenia).

- The application teaches the number of cells that must be administered to produce therapeutic levels of dopamine. *See, e.g.*, page 23, lines 7-10 (10^3-10^7 cells, preferably 10^5 to 10^6 cells, should be used). Watts et al (Neurology (2001), 56(8), Supp.3, P04.102) (of record) provide post-filing evidence that these teachings of the specification are correct. As discussed below, the specification also discloses appropriate types of cells and types of support matrices, and how to make and use them.

35 U.S.C. 112, first paragraph requires that the specification, when filed, contains sufficient information regarding the subject matter of the claims to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. MPEP § 2164.01; *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); MPEP § 2164.04. The examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). Determining enablement is a question of law based on underlying factual findings. MPEP § 2164.01. Any conclusion of non-enablement must be based on evidence as a whole. MPEP § 2164.01(a); *In re Wands*, 858 F.2d 731, 738 (Fed. Cir. 1988). The Examiner must provide specific technical reasons for any enablement rejection; and should never make the determination based on personal opinion. MPEP § 2164.05.

First, the claims as amended herein are limited to a method of administration of retinal pigment epithelium (RPE) cells or chromaffin cells. Support for the amended claims can be found, for instance, in Examples 1 and 2 of the instant specification disclose administration of PCP and fluphenazine to Vervet monkeys followed by administration of human RPE cells adhered to crosslinked gelatin microspheres. See, for example, page 25, line 1 to page 27, line 5 of the specification. The specification also teaches that chromaffin cells can be used in the claimed

invention. See, for example, page 13, lines 23-24. The art at the time of filing also contains numerous reports of administration of dopamine-producing RPE cells or chromaffin cells adhered to a matrix to specific areas of the brain to obtain *in vivo* expression of therapeutically effective amounts of dopamine. *See* Footnote 1, *infra.*

In addition, the specification provides considerable guidance to practice the claimed invention. As Applicants have already noted, the specification provides extensive teaching to one of skill in the art to make and use the invention. The specification teaches types of cells and types of support matrices appropriate for use in the claimed method. See, for example, page 12, line 25 to page 21, line 13. The specification teaches how to make the claimed cell support complex. See, for example, page 21, line 15, to page 22, line 6. The specification teaches how to administer of the claimed cell/support complex to the prefrontal cortex of a patient with schizophrenia. See, for example, page 22, line 11 to page 23, line 21. The specification provides guidelines as to site and means of administration of the complex using sterotaxic surgery. See, for example, page 22, line 8 to page 23, line 11. The specification also provides specific guidance as to the number of cells to be administered to the patient. See, for example, page 23, lines 3-11. The specification also describes examples of negative symptoms of schizophrenia and standard methodology by which the symptoms may be assessed so that alleviation of a negative symptom can be determined. See, for example, page 7, line 21, to page 8, line 4, and page 23, lines 22-31. As discussed, the Examiner is required to provide specific technical reasons why the above-cited portions of the specification allegedly fail to enable the claimed invention, but she has not done so. Applicants respectfully request the Examiner to clarify why the guidance in the specification is concluded to be inadequate.

In the pending Office Action, however, the Examiner persists in the view that "development of cell therapy protocols has been an enormous challenge," and argues that "[c]onsiderable experimentation" would be required to actually provide an enabled protocol for achieving the desired treatment effect. Pending Office Action, at 4. "In view of the state of the art and unpredictability in the art, for reasons of record, such experimentation is not considered routine, but rather would rise to the level of undue experimentation." *Id.* at 4-5.

Applicants respectfully disagree. As explained, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Lengthy and complex experimentation is not necessarily undue, if the art typically engages in such experimentation. *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Applicants respectfully submit that the burden is on the Examiner to establish a reasonable basis to question the enablement provided for the claimed invention; and in order to be reasonable, the rejection must be objectively based on evidence as a whole, rather than personal opinion. The Examiner has produced no evidence that would offset the extensive evidence in the art at the time of filing showing that at the time of filing, cell-based therapy had developed to the point where administering dopamine-producing cells adhered to a matrix into specific areas of the brain to obtain *in vivo* expression of therapeutically effective amounts of dopamine was an established procedure.[2] Applicants respectfully request the Examiner to indicate if there is *any* reference or other evidence that would establish a reasonable basis for the conclusion that the claimed invention would require undue experimentation. Alternatively, Applicants would be grateful if the Examiner could supply an affidavit taking official notice that it would require undue experimentation to practice the claimed invention at the time of filing.

Applicants respectfully disagree with the Examiner's assertion that although the art at the time of filing discloses cellular dopamine replacement therapy for *Parkinson's disease*, it does not provide guidance for treatment of a patient with *schizophrenia*, which has its own distinct etiology. To start with, the Examiner's burden to provide a reasonable basis for a rejection for nonenablement cannot be met by pure speculation. There is absolutely no reason to expect that the level of dopamine expression attainable in a Parkinson's disease patient is any different from that attainable in a patient with schizophrenia, and the burden is on the Examiner to show a reasonable

[2] In her initial Office Action, the Examiner had cited various references discussing the undeveloped state of gene therapy, but these references were published no later than June 1997. Office Action of May 7, 2001, at 4-5. However, the instant application was filed in April, 1999 (and does not claim priority to any earlier application). Enablement must be judged as of the filing date of the application. MPEP § 2164.05(a). The supporting references cited in Footnote 1 were published after June 1997, but before the filing date of the instant application. These references report successful administration of dopamine-producing cells/support complex to produce a therapeutic effect in Parkinson's disease models.

basis for such a conclusion. The Examiner attempts to do this by asserting that schizophrenia is different from Parkinson's disease, having "its own distinct etiology." Pending Office Action at page 4, last paragraph. This begs the question. Even if schizophrenia is a disease distinct from Parkinson's disease, this does not provide any basis to conclude that cell-based therapy suitable for treatment of Parkinson's disease would have **no** effect at all in the treatment of schizophrenia. Applicants again request the Examiner to indicate if there is *any* reference or other evidence that supports this conclusory assertion. Alternatively, Applicants would be grateful if the Examiner could supply an affidavit taking official notice that a cellular dopamine-replacement therapy for Parkinson's disease cannot enable a similar treatment method for schizophrenia.

In addition, the art at the time of filing contradicts the Examiner's assertions. For instance, Davis *et al.*, of record, note that the "clinical similarities" between Parkinson's disease and schizophrenia provides "indirect evidence" that dopamine tone is decreased in some schizophrenia patients, and that "the cognitive and motivational defects in patients with Parkinson's disease symptoms are strikingly similar" to the negative symptoms of schizophrenia. *See* page 1480, column 2. Both Parkinson's disease as well as the negative symptoms of schizophrenia are caused by decreased dopamine tone. Given that the two diseases both involve similar *symptoms* and the same underlying cause (*i.e.*, decreased dopamine tone), the Examiner's assertion that the required dosages are likely to be different simply because the two diseases have a different etiology lacks a reasonable basis.

Moreover, ***doses of dopamine precursors required to produce a therapeutic effect in Parkinson's disease treatment are also effective to alleviate the negative symptoms of schizophrenia***. *Compare* Physician's Desk Reference (1-8 gm of levodopa should be administered daily for Parkinson's disease) *with* Inanaga et al, *Folia Psychiatr Neurol Jpn* (1975), 29:123-43 (400-1200 mgs of levodopa are effective to alleviate symptoms of schizophrenia). Thus, a conclusory assertion that a cellular dopamine replacement therapy for Parkinson's disease could not be effective for treatment of schizophrenia, especially in the face of evidence to the contrary, is not enough to meet the Examiner's burden to provide a reasonable basis for a rejection due to nonenablement. Applicants request Examiner to indicate any evidence that supports her assertion.

Alternatively, Applicants would be grateful if the Examiner could supply an affidavit taking official notice of her assertion.

Moreover, the specification would still be enabling even assuming that treatment of schizophrenia required more dopamine-producing cells than treatment of Parkinson's, as Examiner asserts. Specifically, the application teaches that 10^3-10^7 cells are administered per site, preferably 10^5 to 10^6 cells per site. See, *e.g.*, page 23, lines 7-10. It is not necessary to exactly specify the particular dosage if such a determination is within the ordinary skill. MPEP § 2164.01(c); *In re Bundy*, 642 F.2d 430, 434 (C.C.P.A. 1981) (finding a disclosure that suggested a very broad range of possible dosage for a drug to be enabling, because it was within ordinary skill in the art to determine the specific dosages required for various biological purposes). Even lengthy and complex experiments need not be undue if they are merely routine. MPEP § 2164.05(b). The specification teaches that the exact number of cells to be administered to a particular subject will depend on a number of individual variables that would be apparent to those skilled in the art. *See, e.g.*, page 23, lines 3-5. Watts et al (2001) provide post-filing evidence that these teachings of the specification are correct.

Lastly, the Examiner appears to suggest that cell-based therapy for Parkinson's disease is not enabling for a similar cell-based therapy for schizophrenia because the sites of administration are different. Office Action at 4. Applicants respectfully disagree. The specification teaches with great precision that the cell-support complex must be administered to the prefrontal cortex, particularly the dorsolateral prefrontal cortex, to alleviate cognitive deficits associated with schizophrenia. *See, e.g.*, page 22, lines 13-16.

Thus, the weight of the evidence clearly shows that in light of the teachings of the art at the time of filing, the instant specification would have enabled a skilled person to make and use the claimed invention. The Examiner's assertion that any required experimentation would be undue lacks *any* factual support, and even ignores the clear teaching of the art at the time of filing at the time the instant application was filed. Again, the burden is on the Examiner to establish a reasonable basis for a conclusion of non-enablement. Applicants request Examiner to indicate if

there is *any* reference or other evidence that supports the Examiner's assertion that in view of the state of the art and unpredictability in the art, undue experimentation would be needed to practice the claimed invention. Alternatively, Applicants would be grateful if the Examiner could supply an affidavit taking official notice that any required experimentation relating to the claimed invention would be undue.

In sum, Applicants submit that the pending claims fall within the subject matter that is described and enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

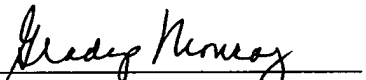
CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 13, 2006

Respectfully submitted,

By 

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